# THE EFFECT OF VITAMINES AND HORMONES ON THE PERIPHERAL CIRCULATION

Thesis

by

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# I INTRODUCTION

The general metabolic effects of vitamines and hormones have been but recently established. Their exact influences on specific body tissues however are still very much in question. The controversy in this regard is one due chiefly to the many difficulties inherent in the study of living tissue. It is not surprising therefore that investigators in this field have arrived at conflicting conclusions.

It is the purpose of this thesis to review the literature concerning the topic "The Effect of Vitamines and Hormones on the Peripheral Circulation". For purposes of orientation, the topic is introduced with a description of the vascular bed and the natural variations which occur in blood flow. A list of animals and tissues used and methods of investigation are discussed. The hormonal and vitaminogenic effects on peripheral circulation are then discussed separately. Inferences and conclusions are made and suggestions are set forth regarding possibilities of future experimentation.

## II DESCRIPTION OF THE VASCULAR BED

Direct observation of the vascular bed appears to be the most satisfactory method of studying the peripheral circulation under the influence of vitamines and hormones. Experimental techniques will be discussed under a following subtopic.

In the vascular bed, the muscular arterioles which lead from the main arteries divide into a number of precapillaries (Fulton and Lutz, 1940) or meta-arterioles (Chambers and Zweifach, 1946). These further divide into the true capillaries which Best and Taylor (1945) define as "all the purely endothelial tubing which lies between the arterioles on the one hand and the small veins on the other." The capillaries which constitute the bulk of the bed lead into the collecting venules which carry the blood into the veins. Chambers and Zweifach (1936) also describe a "thoroughfare" channel of which the true capillaries are offshoots. They have observed in resting tissue, an increase in vasomotion followed by a flow of blood in these central channels with only occasionally a sporadic flow in the true capillaries. During ischemia, for example, this channel

assumes the flow of the entire bed. Grant (1930) has observed that short vessels connecting arterioles with corresponding venules are normally present in the rabbit's ear and in human skin. He called these communicating channels, through which the blood may be shunted, arterio-venous anastomoses.

The mechanism which regulates arteriolar blood flow has been established. That which controls flow of blood in the capillaries is still in question. Bensley and Vimtrup (1928) continuing the work of Krogh discussed the contractile nature of the pericapillary cells known as Rouget Cells. Vimtrup observed the contraction of Rouget cells in Amphibia causing folding of the endothelium. Sandison (1932) found that the Rouget cells on the capillaries of the rabbit's ear showed no evidence of ability to contract and exerted no significant effect in regulating the circulation. Beecher (1936) using the rabbit's ear confirmed the findings of Vimtrup. He noted that the lumen of capillaries was often blocked by the swelling of endothelial nuclei.

Using transparent chambers in the rabbit's ear, Clark and Clark (1940) arrived at the opposite

conclusion; namely that the Rouget cells are non contractile. Previously they had obtained similar results with Amphibians. Zweifach (1934 and 1936) concluded that the pericapillary cells were non muscular and resemble connective tissue cells when he noticed no contraction upon direct stimulation of the vessels with a microneedle. Capillary beds in the frog and mouse were observed. The endothelial nucleus swelled and protruded into the lumen of the vessel when the endothelium was stimulated mechanically. A localized constriction of the capillary walls followed. The stimulation was expecially effective when applied at the nuclear nodes. He also observed that dilation and constriction of the arterioles was followed by the passive opening and closing of "valve like folds of endothelium" at the junction where the capillary branches from the arteriole.

Using the retrolingual membrane of the pithed frog for observation, prepared according to the method of Pratt and Reid (1930), Fulton and Lutz (1940 and 1942) offered convincing proof that the contractile elements of capillaries were found only at the capillary origins. Stimulation with a micro-electrode along the capillary wall produced no effect whereas stimulation of the smooth

muscle cells at the origins resulted in a sphincter like constriction. The response was not affected by the arteriolar or precapillary activity at the time. These investigators found evidence supporting the concept of a smooth muscle motor unit, but they hesitated to say whether the units or individual fibers yielded to an all or none response. It is interesting to note the possible conflict of opinion between these findings and those of Eccles and Magladery (1937) which indicate that smooth muscle cells act all or none whether in single fiber or motor unit form.

Woolard (1926) noticed a loose investment of non-medullated nerve filaments in the capillary area. According to his observations, none ended upon the capillary wall. This sympathetic plexus is considered to be "physiologically discontinuous" by Fulton and Lutz (1942). Krogh (1920) stimulated the sympathetic fibers in the frog's web. The capillaries contracted. If the constrictor tone was eliminated by section of the sciatic or excision of the sympathetic ganglia in the abdominal region, dilation resulted. The existence of dilator fibers has been debated and most investigators adhere to the view that a chemical intermediary substance brings

about the opening of the capillaries. Innervation will be discussed further under the next topic.

## III NATURAL VARIATIONS IN BLOOD FLOW

Krogh (1921) found more vessels open in active than resting tissue in his observations on the skin and web of the frog. Lewis (1926) however noted little change in the capillary pattern of the human skin suggesting that these channels must dilate when blood flow is augmented.

That the capillaries are able to regulate their blood flow has been established earlier by Krogh (1920) and later by Fulton and Lutz (1940). Fulton, Jackson and Lutz (1946) frequently observed two types of spontaneous intermittency of blood flow in the small vessels of the hamster cheek pouch. One type was similar to that observed in the frog's retrolingual membrane, (Fulton and Lutz,1942) resulting from the sphincteric activity at the precapillary junctions. The direction of blood flow was seen to reverse in some capillaries. This type was probably due to changes in the pressure differential between the ends

of the capillary.

Chambers and Zweifach (1946) also reported changes in the caliber of the vessels and suggested that the extent and distribution of the capillary bed wad controlled by vasomotion, occuring at intervals of fifteen seconds to three minutes depending on local conditions in the tissue. In resting tissue, the phase is augmented, the blood flow becoming continuous only in central channels and sporadic in the true capillaries. During the mechanical irritation, the opposite is noted; vasomotion ceases, meta-arterioles and precapillary sphincters open and the capillary bed becomes flooded with blood and hyperemia exists.

Since the early discovery of intermittent capillary flow by Lewis (1927) and Krogh (1929), other workers have made similar observations. In the arteriolar origin of the capillary loops in the epidermal papillae at the base of the human finger nail, moment to moment changes in caliber take place according to Crawford (1926). Grant (1930) noted alterations of blood flow in the vessels of the rabbit's ear after mechanical injury. Wyman and Tum Suden (1932) observing the vessels in the serous mem-

brane of the rat's intestine witnessed a change in caliber of arterioles every few seconds. Burton and Taylor (1936) observed further variations of a few seconds to three minutes in the vessels of the rabbit's ear through a transparent chamber. The plethysmograph records of the digits in the human hand by Hertzman (1941) indicated that recurrent vasomotion was normal. Nicoll and Webb (1946) noted an active and a passive vasomotion in the wing membrane vessels of the bat. The former was said to be due to the muscular components especially in the precapillary sphincters, the latter to alterations in pressure. These observations are in agreement with the earlier observations of Fulton, Jackson and Lutz (1945). Chambers (1948) confirmed these results indicating local tissue conditions were very important in regulating peripheral circulation. Vasomotion was the controlling factor. The thoroughfare channels and precapillary offshoots were seen to relax and contract spontaneously from minute to minute, responding to different physiological conditions. When vasomotion was slight, the precapillaries remained open, spreading the blood flow through the capillary bed. Active vasomotion produced a rapid flow through the preferential channels only. Chambers and Zweifach (1944 and 1948) examining the vessels of the rat's mesoappendix and the

dog's omentum reported intermittent activity of thirty seconds to three minutes at the precapillary sphincters.

Burton and Taylor (1939) further suggested that vasomotion depended on nerve control. This was later confirmed by Chambers and Zweifach (1946). Nicoll and Webb (1946) however evidenced a continuance of vasomotion after denervation. The rhythmical beat observed by Fulton and Lutz (1940) in restricted vascular areas indicated that a neuro-motor mechanism controlled the small blood vessels of the frog. The perivascular plexus appeared to be composed of vasodilator and vasoconstrictor fibers, since the stimulation of certain fibers yielded an individual response. In 1942, they reported a diphasic response to nerve stimulation, dilation followed by constriction. Further investigation revealed that rather than a continuous muscle syncitium as was reported by Bozler (1939) in mammalian uteri, muscular elements were confined to the points of union between the particular vessels. As early as 1909, McGill had offered proof for a partial syncitium in mammalian vascular smooth muscle.

The importance of maintaining normal vasomotion is evident. Such a delicate mechanism may easily

be disturbed when preparing tissue for observation. The natural behavior of the vessels is disturbed by only slight trauma, (Chambers and Zweifach 1947,1948). Occasionally slight edema may be evident under such circumstances (Chambers, 1948). Care in tissue preparation therefore is vital in obtaining controlled conditions.

## IV LIST OF ANIMALS AND TISSUES USED

The vascular beds of the following tissues and organs have been observed by various investigators in studies of vitamin and hormone action:

1. Skin, web and retrolingual membrane of the frog.
2. Rabbit's ear.
3. Rat's mesoappendix and endometrium.
4. Dog's omentum.
5. Cat's mesentery.
6. Cheek and pouch of the golden hamster.
7. Bat's wing.
8. Guinea pig mesentery.
9. Mammalian interdigital web.

10. Sexual skin and nasal skin of the monkey.
11. Human nail bed.

Pitressin was applied to cutaneous capillaries in:

1. Leg of hypophysectomized frog.
2. Web of frog.
3. Dogs.
4. Cats.
5. Rabbits.

Epinephrine was applied to vessels of:

1. Frog skin, web and mesentery.
2. Rat mesoappendix.
3. Rabbit's ear.
4. Guinea pig mesentery.
5. Dog muscle and omentum.
6. Cat mesentery.

Epinephrine was also administered following thyroidectomy and adrenalectomy.

Adrenal cortical hormones were given to:

1. Scorbutic rats, guinea pigs and rabbits.
2. Adrenalectomized dogs and rats.

Adrenotropic hormone was administered to:

1. Guinea pigs.
2. Rats.

Estrogenic hormones were administered to:

1. Men and women
2. Dogs.
3. Rabbits.
4. Monkeys.
5. Rats.
6. Cats.

Niacin was used with normal subjects and with pellagrins.

Ascorbic acid treatment was used on rabbits and rats and guinea pigs.

Vitamin P was used on:

1. Guinea pigs.
2. Rabbits.
3. Rats.
4. Man

Studies were made of riboflavin deficiency in:

1. Swine.
2. Albino mice.

3. Men and women.

Thiamine deficiency was studied in men.

Ascorbic acid deficiency was studied in:

1. Rats.
2. Guinea pigs.

## V METHODS OF INVESTIGATION

### A. Instrumentation

A popular method of observing the small blood vessels of the rabbit's ear was introduced by Sandison in 1924. A transparent window is inserted several days before experimentation. It offers a satisfactory means of direct visualization of the peripheral circulation and has been used by the following investigators:

1. Grant, 1930
2. Sandison, 1932
3. Clark, Clark and Williams, 1934
4. Clark &Clark, 1934 and 1940
5. Wilson, 1935
6. Beecher, 1936
7. Reynolds and Foster, 1937, 1940 and 1941

8. Rigdon, 1940
9. Rigdon and Chrisman, 1941
10. Abell and Page, 1942
11. Lewison and Essex, 1943
12. Chambers and Copley, 1947

Pratt and Reid in 1930 instituted a method for working on the terminal nerve muscle units in the retrolingual membrane of the frog. The vascular bed of the pithed frog is illuminated by transmitted light. This preparation is an excellent way to observe the vascular bed and was used by Fulton and Lutz in 1940 and 1942. Other tissues were prepared in a similar manner for direct visualization of the small blood vessels, for example:

The skin and web of the frog; Krogh, 1921
The dog's omentum; Chambers and Zweifach, 1948;
    Zweifach, Lee, Hyman and Chambers, 1944
Rat mesoappendix; Chambers and Zweifach, 1948
Hamster cheek pouch; Fulton, Jackson and Lutz,
    1945
Nasal mucosa and sexual skin of the monkey;
    Collings, 1926; Akroyd and Zukerman, 1938;
    Mortimer, Wright, Bachman and Collip, 1938
The capillary loops of human skin; Carloni, 1930;

Harpuder, Byer and Stein, 1947; Abramson,
Katzenstein and Senior, 1940

Plethysmograph records of finger volume were used as indication of digital or radial blood flow by Eichna and Bordley (1942), Reynolds and Foster (1937, 1939, 1942) and Harpuder and Byer (1947). In 1947 Burch described a new portable type of instrument. Cruikshank and Whitfield (1945) introduced a new technique for estimating the blood volume by using the dye T 1824.

In the experiments determining permeability of the capillaries, intravenous injection of Trypan blue was commonly used. The filtration of the stain from the circulating blood was used as an indicator by:

Menkin, 1940
Freed and Linder, 1941
Rigdon and Chrisman, 1941
Hechter, Krohn and Harris, 1942
Shleser and Freed, 1942
Fine and Fischman, 1942
Graham, 1943

## B. Administration of Hormones and Vitamines

Estrone (theelin), estradiol (usually in the

benzoate form), stilbestrol (the diethyl type), progestrone and the proprionic ester of testosterone were injected intramuscularly, subcutaneously or intravenously. Occasionally oral doses were given to women, and dogs; in each case the dose being three or four times larger than by other types of administration. An aqueous solution of estrone gave a more prolonged effect than an oil solution in producing estrus in rats (Grollman, Harrison and Williams, 1940). It may also be more effective in producing vascular effects although no such evidence is given.

The dosage varied according to the subject, frequency of administration, type of injection and hormone used in each experiment. The human dosage varied from 10,000 international units to 10,000 rat units daily, when the hormone was stilbestrol and estrone respectively. It is now widely accepted that one rat unit is approximately equal to ten international units. Dogs were given five to ten milligrams daily; monkeys were given ten milligrams daily; rats were given ten to twenty rat units when estradiol benzoate was used. Comparison of dosage may be made according to the following scheme: one milligram of estrone equals ten thousand international units; estradiol benzoate had a potency of 6,000 rat units

per milligram, one milligram of diethylstilbestrol is equal to twenty thousand international estrone units. It therefore follows that five milligrams of diethylstilbestrol has approximately the same estrogenic potency as one and two thirds milligrams of estradiol benzoate or ten milligrams of estrone (MacBryde, Castrodale, Helwig and Bierbaum, 1942). To produce the same effect as an intramuscular dose equivalent to 100,000 international estrone units, an oral dose four times as large had to be administered. It was difficult to estimate what could be considered an effective dose since most of the papers read gave scanty information concerning it. Vague statements such as "Large doses of estrogens were given" were typical.

Krogh (1926) introduced subcutaneously minute drops of pituitrin diluted 1:100 to obtain an effect on the web vessels of the frog. Levinson and Essex (1943) made dilutions of pitressin with physiological saline solution to obtain a strength of 2.0 pressor units per cubic centimeter. The mixture was made just prior to injection into marginal vessels of the rabbit's ear and given in doses of 0.1 pressor units per kilogram of body weight. At intervals of 10 to 15 minutes, four doses were given. Woodbury and Ahlquist (1946) also used intravenous

injections. Abell and Page (1942) achieved similar effects with 0.6 units. Other investigators like Wilson (1935) diluting with sterile Ringer's solution used varying dilutions of 0.5 to 5 mg.

Sandison (1932) used 1:100,000 dilution of adrenalin for intravenous injections in the marginal vessel of the rabbit's ear. This is the same dose Levy (1916) and Lutz and Wyman (1925) administered to test its sensitization on the sympathetic nerves of the cat. Lee and Lee (1947), Landis (1946), Chambers and Zweifach (1944, 1947), and Danilopolu (1946) used topically applied epinephrine but made no mention of amount. Griffith, Omachi, Lockwood and Loomis (1947) made one cubic centimeter injections per minute in the jugular of the anaesthetized cat. Harpuder, Byer and Stein (1947) used intrarterial injections of adrenalin, the doses varying from 0.0002 µg. to 0.05 µg. when measuring the effect on the blood vessels in the human forearm. Parrot and Lavolly (1944) injected intraperitoneally in guinea pigs and intramuscularly in man. Levinson and Essex (1943) found that 0.05 cubic centimeter of 1:1,000,000 solution in the marginal vein of the rabbit was effective; 1:1,000 especially effective. Abell and Page (1942) administered 0.0015 mg. to 0.10 mg. intrave-

nously. Grant (1930) used dilutions of 1:10,000 to 1:1,000 for the chloride. Wider variations of strength were used by Wilson (1935) of 1:20,000 to 1:10. Meidinger (1946) found adrenaline ascorbate and adrenaline hydrochloride equally effective.

Fouts, Helmer, Lepkovsky and Jukes (1937) administered 500mg of nicotinic acid orally to normal and pellagrin subjects. Smith, Ruffin and Smith (1937) chose to give intramuscular injections of 60 mg. and intravenous injections of 12mg. In 1938 Sebrell and Butler achieved results with as little as 30 to 50 mg. oral doses daily. Sydenstricher, Schmidt and Fulton (1938); Spies, Cooper and Blankenhorn (1938); France, Bates, Barker and Matthews (1938) all used oral administration. Spies, Hightower and Hubbard (1940) reported using large doses while Abramson, Katsenstein and Senior (1940) gave 200 mg. orally or 5 to 25 mg. intravenously. In 1941 Loman, Rinkel and Myerson experimented with injections into the basilic vein or carotid artery of doses varying from 12.5 to 50 mg.

Vitamin C was administered orally and parenterally to scorbutic guinea pigs by Menkin, Wollbach and Menkin (1934) and Wollbach (1937) and again orally to man

by Wollbach and Bessy (1942). The oral doses were reported to be larger.

In treating increased capillary fragility, vitamin P was given orally to guinea pigs by Bourne (1943), to man by Scarborough (1945) and Shanno (1946) and to rabbits by Ambrose and Deeds (1947). Vitamin P was applied topically on the rat's mesoappendix by Haley, Clark, Geisman (1947) and the vascular effects were noted in each case.

In order to establish the association between the two vitamins, Gabe and Parrot (1948) gave large oral doses of both C and P to rats and guinea pigs. In a second experiment Cotreau, Gabe, Géro and Parrot (1948) used 10 mg. of ascorbic acid along with large doses of vitamin P in tests with guinea pigs.

C. Endocrine Ablation

In a series of experiments by Swingle, Vars and Parkins (1934), Parkins, Taylor and Swingle (1935) and Swingle, Parkins, Taylor and Hays (1936, 1937,1938), dogs were adrenalectomized to note the effect on capil-

lary tone. Swingle, Parkins and Taylor (1938) also Cope, Brenizer and Polderman (1942) adrenalectomized dogs previous to administering adrenal cortical secretions. Before the administration of ACTH, the adrenals in rats were removed by Sayers and Sayers (1945, 1947) and by Shorr, Zweifach and Furchgott (1947).

Hypophysectomy of frogs was practiced by Krogh and Harrop (1921), Krogh and Rheberg (1922) and by Krogh (1926) in a series of experiments indicating its effect on capillary tone. Heinbecker (1948) used hypophysectomized dogs to denote the sensitivity of blood vessels to epinephrine and desoxycorticosterone. Hypophysectomized rats were used by Sayers, Sayers and Woodbury (1948) to reveal the effect of ablation on the ascorbic acid content of the adrenals.

## VI OBSERVATIONS

### A. Hormones

#### 1. Posterior Pituitary

In 1921 Krogh and Harrop postulated the theory

that capillary tonus was maintained by a substance present in the circualting blood of frogs and mammals. The probability that this principle was liberated from the posterior pituitary was suggested. The substance was shown to have chemical reactions similar to those of the active principle of the pituitary.

These views were strengthened by several investigations performed by Krogh and Rheberg (1922). Twenty four hours after the removal of the posterior lobe of the pituitary from Rana temporania, the capillaries in the skin and web were strongly dilated and the circulation was sluggish. Since these effects did not result from the removal of the glandular portion of the pituitary alone, it was inferred that the "capillary hormone" did not have its origin here. Further experiments demonstrated that injection of strong solutions of pituitary extract (pituitrin) into the web of the frog produced a constriction of the arteries and capillaries whereas introduction of minute droplets caused contraction of the neighboring capillaries without affecting the arteries. Krogh (1926) compared the pigmentary reactions of the skin of the frog to different concentrations of pituitary hormone by perfusing the two legs with different dilutions. Once

again he confirmed his previous results indicating that the characteristic action of the pituitary posterior lobe principle is to sustain the tonus of the capillaries. It is interesting to note that the posterior lobe extracts exert even a stronger effect on the capillaries than they do on the arteries. Dilutions of such a strength as to not affect arterial tone have a very definite effect in the frog on the capillary tone; hence the term "capillary hormone". Its specific chemical nature is yet to be determined. Indeed actual proof that such a substance is secreted into blood or lymph is yet lacking.

Wilson (1939) reported a constriction of arteries injected with 0.5 to 5 mg, solutions of pressor material from the posterior lobe (vasopressin) diluted with sterile Ringer's solution. Her injections were made into the marginal vein of the rabbit's ear. Changes in the caliber of the veins seldom occurred. As far as could be determined, pitressin never seemed to initiate rhythmic contraction. No statement regarding the capillaries was made.

Abell and Page (1942) stated that although pitressin was capable of constricting the arteries and

arterioles of the rabbit's ear, reducing blood flow severely; arteriolar pressure was elevated but slightly. The injections were followed in 20 to 30 seconds by halting of the circulation for approximatelyfive minutes due to arteriolar constriction. Independent capillary constriction was not apparent; no lumens were seen to close. The response was much the same in the denervated ear. It was suggested that the ability of pressor substances to cause vasoconstriction varies greatly in different parts of the vascular system.

Under excellently controlled conditions, Levinson and Essex (1943) noted the effect of pitressin on the vessels of the rabbit's ear through transparent chambers. Within 20 seconds after injection, powerful constriction of arterioles was apparent, the maximal effect lasting three to ten minutes. Again individual constriction of capillaries was not observed.

The hypothesis that pitressin raises the blood pressure was presented by Woodbury and Ahlquist (1946). However it was noted that cutaneous warmth was experienced by some patients after intravenous injections of pitressin. Pulse curves of cats following administration of

pitressin have indicated vasodilation. Following intravenous injections in dogs, the blood flow through cutaneous vessels increased as a result of the rise in arterial pressure and dilation of cutaneous vessels, whereas in muscular tissue, the opposite response occurred. Different conditions, species and individual dogs demonstrated variation in the amount of cutaneous vasodilation. Severing of the supplying nerves produced no change. It was found that pitressin induced a vasoconstrictive effect in rabbits and that the blood vessels became more sensitive to the peripheral vasoconstrictive action of pitressin after nerve degeneration. A dilatory blood flow in the denervated skinless frog's leg followed intravenous injection of pitressin. These observations indicate that this substance has the potentiality of producing either response in cutaneous vessels, ie. dilation or constriction.

2. Adrenal

a. Medulla

After the cervical sympathetic in the neck of cats is stimulated, adrenin is 200 to 300 percent more

effective in augmenting the arterial pressure (Levy,1916). This does not occur if the thyroid glands are extirpated before the investigation is made. In the presence of the thyroids and upon their stimulation, the sympathetic nerve endings become more sensitive to the action of adrenalin. In 1925, Lutz and Wyman resumed these studies. A rise in pressure was found to come about after the removal of the adrenals and the thyroid glands.

Krogh (1921) found that whereas the constrictor action of pitressin was confined to the capillaries of the frog's skin and web, that of adrenalin was effected on the arterioles and arteries. The exact function of these two hormones was questioned.

The effect of various dilutions of adrenaline chloride on the normal and denervated ear of the rabbit was examined by Grant (1930). A marked constriction originating at the point of injection traveled up and down the artery obliterating the lumen of the vessel. Local rhythmic oscillations in caliber commenced shortly previous to maximum extension. Sandison (1932) noted the arteries and arterioles of the rabbit's ear constricting following the intravenous injection of 1:100,000 concentration of

adrenaline. The capillaries remained unchanged; the flow of blood within depending on existing conditions in the neighboring arterioles. Using similar experimental conditions, Wilson (1935) found that constrictor effects varied from slight to intense according to the strength of adrenaline chloride used. Rigdon (1940) proposed that epinephrine be used to check the exudation of blood corpuscles and plasma because it exhibits arteriolar constriction. No conclusive experiments have been performed showing epinephrine's specific effect on capillary permeability. Landis (1946) found that epinephrine lessens local edema. Abell and Page (1942) observed arteriolar narrowing but the capillary lumens remained open.

The typical epinephrine response was recorded by Levinson and Essex (1943) in the rabbit's ear, occurring within 20 seconds after the injection. The reaction varied in intensity from one arteriole to the other although the dose was the same in each case. Occasionally small doses initiated constrictions at irregular intervals along the arterioles giving the vessel an "appearance of a string of sausages". This conception lends support to the smooth muscle motor unit theory of Fulton and Lutz (1942). Maximal constriction occurred over a period of

time varying from thirty seconds to sixty seconds. Often relaxation of the vessel followed by dilation for a few seconds occurred. A concommitant narrowing of lumina of venules was noted, but this was a weak response. The capillaries on the other hand were devoid of activity, remaining open as long as blood was received from the arterioles. After denervation of the ear, a diminished dose of epinephrine was just as effective in producing the desired response. Initiation of the action in this case was slower, but of longer duration. Once again no adequate explanation was given to account for the increase in sensitivity to epinephrine and the return of "vascular tone" following denervation.

The periodic vasomotion of metarterioles and precapillaries and their susceptibility to chemical changes in the immediate tissue area is significant, (Chambers and Zweifach, 1944). Their reactivity to epinephrine was reported.

Danielopolu (1946) observed that small doses of epinephrine caused vasodilation whereas large doses produced the vasoconstrictor response, "agissant sur la cellule de l'organe terminal". The studies of Griffith,

Omachi and Lockwood (1947) indicate that either effect may occur depending on the rate of injection or uncontrollable conditions in the surrounding medium. Intrajugular injections of adrenalin were used to note the effect on the blood flow through the hind limb or resting muscle of anaesthetized rats. Harpuder, Byer, and Stein (1947) recorded measurements of blood flow in the human forearm following intra-arterial injections of epinephrine. Doses from 0.002 µg. to 0.05 µg. into the brachial artery initiated an immediate **rise** in blood flow suggesting vasodilation sometimes followed by vasoconstriction, whereas doses of one to two µg. lowered the blood flow locally. As far as could be determined, doses of 0.05 to 0.1 gamma were ineffective. The concept of threshold activity implies the existence of vasodilator and vasoconstrictor mechanisms.

In describing the capillary bed, Chambers and Zweifach (1946) reported that the muscular constituents especially the metarterioles and the precapillaries are particularly affected by epinephrine stimulation. The observations of Chambers and Zweifach (1947) indicate, too,a definite point of concentration at which the musculature of the normal capillary bed responds to epine-

phrine. It is suggested that a vasoconstrictor material causes the muscular components to bedome more sensitive to the hormone. A vaso-depressor substance would initiate the opposite reaction. It was suggested that these vasotropic principles originated from humoral factors and are carried by the blood. In 1948, Chambers and Zweifach confirming the precapillary sphincter concept of Fulton and Lutz (1940, 1942) while observing the capillaries in the dog's omentum noted that the muscular elements here were especially reactive to epinephrine. Minute concentrations which produce no effect on larger blood vessels yielded a definite constrictor response.

Extreme care in preparing tissue for observation and controlled conditions are essential in order to achieve significant results concerning the epinephrine response. The important part humoral factors play in conditioning the reaction has already been mentioned. Induced shock has been shown to heighten the epinephrine response in the peripheral blood vessels of the cat mesentery and dog omentum (Shorr, Zweifach and Furchgott,1947). According to Heinbecker (1937, 1948), failure of the neurohypophysis to function properly renders the blood vessels especially susceptible to the action of epinephrine.

b. Cortex

In a series or experiments on adrenalectomized dogs, Swingle et al. (1934, 1935, 1936, 1937, 1938a, 1938b) proposed that adrenal cortical secretions are necessary to maintain capillary tonus. Adrenalectomy with its concommitant decrease in these hormones is followed by capillary atony with its accompanying dilation of vessels and slackening of the blood current, increased capillary permeability and eventually "perivascular stagnation". Swingle and Remington (1941) went a step further and administered desoxycorticosterone acetate or cortical extract to adrenalectomized dogs. The restoration of vessel permeability was apparent since the ability to retain transfused serum was enhanced.

Menkin (1940) and Cope, Brenizer and Polderman (1942) demonstrated that intra-cutaneous injections of adrenal cortical extracts or desoxycorticosterone acetate decreased capillary permeability in rabbits. The same results were achieved by Freed and Linder (1941) and Shleser and Freed (1942) administering cortical steroids and crystalline corticosterone. Contrary to the findings of Menkin (1940), Fine and Fischmann (1942) using paren-

teral injections of desoxycorticosterone acetate in the rabbit's ear discovered no change in capillary permeability. Hyman and Chambers (1943) found that adrenal cortical extract and 11-desoxycorticosterone reduced edema formation. The criterion used was a decrease in the weight of the perfused hind limbs of the frog. Zweifach, Shorr, Furchgott (1947) presented evidence that cortical hormones had a direct effect on vascular tone. Ablation of the adrenals in rats caused a diminished reactivity of the muscular constituents of the vascular bed. Administration of cortical extracts was found to be very effective in restoring to normal the tonus of these vessels.

Once again the importance of well controlled methods of investigation is to be emphasized. The increased permeability produced by shock, however, can be counteracted by corticoids according to Seyle (1946). Heinbecker (1948) has shown that diminished neurohypophysis function is followed by a heightened sensitivity of the blood vessels to desoxycorticosterone.

### 3. Ovarian

The most detailed work concerning the relationship between the sex hormones and blood vessel activity has been done by Reynolds and Foster and recorded in a series of papers printed from 1937 to 1940. Experiments were performed to demonstrate the peripheral vascular effects of estrogen on the rabbit, human male and female. Observations were made on the trans-illuminated ear of the anaesthetized rabbit given a subcutaneous injection of estrogen. To eliminate the source of estrogen in the organism itself, ovariectomized animals were employed. The minute vessels (arterioles, venules, arterio-venous anastomoses and capillaries) which are indistinct to the naked eye but give rise to the ground color of the ear (Grant, 1930) exhibited dilation within three to twenty minutes after the injection. The effect was characterized by the opening of an extensive network of vessels which may be detected only in fragmentary bits during the pre-injection period. In addition, numerous capillary loops opened and red blood corpuscles were observed trailing through the vessels.

Measurements of the skin temperature showed that at moderate or low room temperature (18 C - 24 C)

the vasodilation took place with either no change in ear temperature or with a fall in skin temperature. Denervation of the ear produced no change in response. This group of small blood vessels resemble qualitatively the blood vessels of the human skin with the exception that the former are more sensitive to changes in temperature. It appears that the ears of the rabbit constitute a primary route for heat loss while in the human such activity occurs over a much larger surface. This factor is significant in evaluating the following. The rate of blood flow through the ear did not increase materially. This rather varies with requirements for heat loss which vasodilation of small vessels impose in the regulation of normal body temperature under experimental conditions. It was clear that on physiological grounds that with an enlarged capillary bed in the ear, the possibility for increased heat loss with less arteriolar vasomotor adjustment was readily possible.

To observe the dermovascular action of estrogen in the human male, intramuscular arm injections of the hormone were administered as unknowns to the subjects. Those responding to corn oil injections were eliminated from the experiment. In three to fifteen minutes, the

finger volume showed a steady increase for a half hour period, occasionally after a transient decrease (vasoconstriction resulting from nervousness at the time of injection). During the period of vasodilation, no perceptible rise in nail bed temperature or in plethysmograph temperature occurred. It was concluded that vasodilation takes place beyond the small arterioles since the volume change is affected without a significant alteration of blood flow.

Women in menopause were studied under similar conditions. One type of response followed that pattern noted in males. In the second, a much more rapid increase could be observed, frequently with an increase in temperature so the conclusion was drawn that arteriolar dilation may occur in such patients. This latter response was observed in women who were nervous before or during the course of the treatment.

Vasodilation occurred both as a dermovascular reaction to estrogen and as a menopausal flush. In the latter, the effect was in part due to arteriolar dilation and in the estrogenic response, the smallest vessels beyond the arterioles were involved. In this case, the

response seemed to be a direct effect of the hormone, whereas in the flush type, intermediation of nervous activity (inhibition of arteriolar tone) was involved.

The tonicity of the cutaneous capillary network had been known to vary with each phase of the menstrual cycle. Carloni (1930) in a series of studies on women during all phases of the menstral cycle as well as the climacteric, administered parenterally specific quantities of follicular extract and corpus luteum extract. Capillary loops, their blood volume, characteristic blood flow and visibility of the subpapillary network were observed before and after administration of the hormone. Modifications presented by the fine vessels were seen with a capillaryscope. The follicular hormone was found to have definite vasodilating and hyposensitive properties. The ascending segment of the capillary loop appeared more voluminous. The reaction was most frequent and of the longest duration in the first phase of the menstrual cycle (that phase in which this hormone is predominating ). After the injection of the luteal hormone, there was a prevalent dilation of the descending segment. This response reached its maximum intensity in the third phase of the cycle. Once again the strongest reaction occurred when the greatest

amount of corresponding hormone was produced.

Carloni indicated that in order for the influence of follicular hormone to be felt during the predominance of a different ovarian hormone, the endocrine stimulation whould necessarily be carried to nervous centers which preside over the innervation of the capillary network. Later work regarding capillaries invalidates his statement that the smooth muscle of capillaries is stimulated directly to dilate.

Direct observation and histological study showed that hyperemia of the sexual skin occurred during phases of estrogenic stimulation in the monkey (Aykroyd and Zuckerman, 1938). High protein content of the interstitial fluid suggested that the capillary bed of the sexual skin became freely permeable under the influence of estrogenic stimulation. The excess tissue fluid in the swollen skin may have been due to increased permeability and consequent diminished effective reabsorption or osmotic pressure of the blood plasma.

Cyclical reddening of the sexual skin in the Rhesus macaque as a result of estrogenic stimulation is

due to the engorgement of a plexus of large thin walled channels that lie just beneath the epidermis (Collings, 1926). He ascribed such swelling to a change in the subepithelial tissues and not to edema, contrary to the later findings of Zuckerman and Parkes (1932) who attributed the tissue swellings to edema. Collings concluded that there is a direct correlation between the degree of reddening of sexual skin and the size and engorgement of the superficial blood vessels. These observations were confirmed by projector tracings of sections of many different regions of the active and inactive sexual skin.

The nasal mucosa of the intact monkey responded to the administration of crystalline estrogenic substances in the manner of and synchronously with the change known to occur in the nipple, sex skin, face and back (Mortimer, Wright, Bachman and Collip, 1936). The effect was produced in both males and females, (castrate or normal) and immature or adult. The response was most obvious in the middle and inferior conchae which showed reddening and/or swelling. In the untreated immature and adult female, peaks of nasal activity normally occur "premenstrual" in time and at intervals of about twenty-eight days. Such naturally occurring nasal cyclical activity was most marked in the autumn months, the mating

season.

Freed and Linder (1941) reported that an increase in capillary permeability followed intracutaneous injections of estrone, stilbestrol and progesterone in the ears of rabbits, Hechter, Krohn and Harris (1942) interpreted an accumulation of dye in the tissue spaces of the uterus and vagina following administration of estrogens and progesterone as an increase in capillary permeability. Rigdon and Chrisman (1941) under similar experimental conditions demonstrated that alpha-estradiol benzoate had no effect.

Reynolds, Hamilton, DiPalma, Hubers and Foster (1942) found that injection of progesterone created a rise in finger volume indicating a dilation of peripheral vessels. These studies of castrate, eunuchoid and normal males showed that they reacted in a similar manner to the normal men and menopausal women of a previous experiment following injection of estradiol benzoate. Vascular changes were evident within an hour, the heightened measurement persisting for about four hours. Normal values were attained about the sixth hour. No significant deviation from the normal of cutaneous capillary circulation could

be noticed by Roberts (1944) during pregnancy ( a time in which the circulating estrogens are increased).

McGrath and Hermann (1946) proposed the clinical use of the estrogens in the treatment of peripheral vascular disease. The therapeutic quality of synthetic estradiols (theelin and alpha estradiol) for the treatment of such disturbances where vasomotor tone has been upset is suggested. The authors believe that dilation due to the estrogens is caused by the local liberation of acetylcholine.

Estrogens including stilbestrol have been known to cause vasodilation of the endometrial blood vessels of the rat (Kayser, 1947). Rhythmical activity of these vessels ceases. Maximum effect is achieved in four and one half to six minutes. The deeper over all red color of the tissue indicated that the existing vessels are dilated and a larger number of capillaries are functional. These investigators present the possibility of a local production of and release of a histamine-like substance which initiates the dilation. It appeared as though the vascular changes were not affected by atropine, invalidating the previous suggestion of McGrath and

Hermann (1946) that acetylcholine is set free and commences the dilatory effect.

### 4. Testicular

The dermovascular action of androgens in castrate, eunuchoid and normal males was studied by Reynolds, Hamilton, DiPalma, Hubert and Foster (1942). The small peripheral vessels of the hypogonadal males showed a significant increase in sensitivity to mechanical stimulation. A very marked increase in finger volume indicating vasodilation was recorded on the plethysmograph, following parenteral injections of testosterone. The vascular effect was apparent within the hour and retained its maximal effect for approximately four hours returning to normal by the sixth hour. The incentive for the use of androgens in peripheral vascular and coronary artery disease has been furnished by the observance of these phenomena.

The uterus and vagina of castrated rats and rabbits were observed by Hechter, Krohn and Harris (1942) following the parenteral injection of testosterone. The enhanced concentration of dye in the tissues denoted an in-

crease in the capillary permeability.

## B. Vitamines

With the exception of a few experiments concerning vitamines D and E, most of the studies conducted regarding the effects of vitamines on peripheral circulation have pertained to the water-soluble group including the B complex (especially thiamine, niacin, and riboflavin), C and P.

### 1. Thiamine

It appears that the effect of thiamine on the peripheral circulation is felt totally through the nerve components. This vitamine plays an important role in the chemical mechanism of nervous excitation, more specifically on the chemical equilibrium of the neurone. Brown and Feldberg (1936) and Feldberg (1943) have shown that the rapid loss of thiamine plus the rapid loss of acetylcholine is one of the first signs of nerve degeneration. The sequence of nerve degeneration due to thiamine deficiency according to Wollbach and Bessy (1942) was from

the periphery to the center. Deterioration of the myelin sheath was gradually followed by degeneration of the axis cylinder. In cases where risk of nerve degeneration is impending, administration of thiamine has been recommended. Roth and Williams (1944) found no indications of vasomotor disturbances in persons suffering from extreme thiamine deficiency.

### 2. Riboflavin and Folic Acid

Only scant information concerning these two members of the B complex could be found in the literature. Roth and Williams (1944) kept a group of healthy women on a diet restricted to 0.7 mg. of riboflavin per day (about half of the usual daily allowance) for two hundred and eighty eight days. No pathological cutaneous changes were detectable.

Folic acid appears to reduce the sensitivity of the cutaneous vessels to estrogens (Hertz 1945). Administrations of maximal doses of stilbestrol produced only slight estrogenic response when the chick's diet was deficient in folic acid. With the addition of this vitamine to the diet, progressive increments in response were recorded.

### 3. Niacin

The dilation of peripheral blood vessels was observed in ten to twenty minutes following the oral administration of five hundred milligrams of nicotinic acid to human pellagrins (Fouts, Helmer, Lepkovsky, Jukes, 1937). A few minutes after the intramuscular injection of sixty milligrams of nicotinic acid, intense flushing of face, neck, chest and arms occurred. The results lasted about fifteen minutes (Smith, Ruffin, Smith, 1937). Similar effects were achieved with the intravenous injections of twelve milligrams. Spies, Cooper and Blankenhorm, (1938) while using nicotinic acid in the treatment of pellagra noticed severe flushing of the face and extremities approximately twenty minutes after administration. France, Bates, Barker and Matthews (1938) witnessed corresponding vasodilatory action in the two pellagra patients treated with nicotinic acid amide and sodium nicotinate. The vasodilator action of niacin was again reported by Sydenstricker, Schmidt and Fulton, (1938) and Sebrell and Butler (1938), this time with smaller oral doses than given in previous experiments (thirty to fifty milligrams). Spies, Hightower and Hubbard (1940) found that the administration of niacin to normal subjects and pellagrins brought

about a flushing of the face and neck as well as a sensation of heat, tingling and itching. Adrenaline reversed this vasodilator action. Administration of niacinamide in high dosage to subjects saturated with niacin did not exhibit peripheral vasodilation, or any other vascular changes as did large doses of niacin. Injections of twelve and one half to fifteen milligrams into the basilic vein, carotid artery or the brachial artery in one or two minutes produced flushing of the skin especially in the face and abdomen, lasting for thirty minutes (Loman, Rinkel, and Myerson, 1941).

Using a plethysmograph for measurement of blood flow in the hand, forearm and leg, Abramson, Katsenstein and Senior (1940) studied the peripheral vascular effects of nicotinic acid. The blood flow was augmented in the parts just mentioned following administration of nicotinic acid, two hundred milligrams orally or five to twenty-five milligrams intravenously. Since there was no alteration in blood pressure or pulse rate, it was suggested that the effect was felt locally by the smallest peripheral vessels. These authors proposed that nicotinic acid be used therapeutically for patients suffering with a diminished blood supply to the extremities.

### 4. Ascorbic Acid

Menkin, Wolbach and Menkin (1934), Wolbach and Bessey (1942), and Chambers and Cameron (1943) have reported the importance of vitamin C in the diet for the maintainance of intercellular cement to retain cohesion between the epithelial cells of the capillary wall. Scorbutic animals were deficient in this interstitial substance. Hemorrhages and petechiae formation and a sluggish blood flow through these vessels were prevalent.

Dalldorf (1933), Dalldorf and Russel (1935), Roberts, Blair and Bailey (1937), Bell, Lazarus and Munro (1940) and Davis (1946) have observed that increase in vascular fragility appears as an early symptom in vitamin C deficiency. According to Holland, Conniff and Burger (1947), normal or near normal concentrations of ascorbic acid must be present in the tissue for the normal functioning of the capillary wall. Farmer (1940) and Crandon, Lind and Dill (1940), also Farmer (1941) in studies chiefly on human ascorbic acid deficiency have found no significant correlation between blood levels of ascorbic acid and tendency of petechiae formation.

The failure of scorbutic animals to withstand trauma or to develop resistance to it is closely related to a visible diminishing vascular reactivity and a "consequent impotence of vaso-compensatory mechanism" (Bessey, Menten and King, 1934 and McDevitt, Duryee and Lowenstein, 1944). Ungar (1943) and DePasqualini (1946) found the pretreatment with ascorbic acid was significant in protecting guinea pigs against trauma. The amounts of ascorbic acid found in capillary blood is very minute (Raoul, 1947 and Vogt, 1948).

Lee and Lee (1947) subjected a group of guinea pigs to experimental scurvy, and then observed the vascular changes of the mesenteric capillary bed directly. The results were as follows: a dilation of the peripheral vascular network was evident; blood flow became sluggish; periodic vasomotion was absent. Blood flow was still continuous in the capillaries. With the exception of the largest arteries, arterioles and precapillary sphincters, the capillary bed did not react to even strong dilutions of epinephrine. Capillary walls appeared intact. Petechiae formation was rare. However, stretching the mesenteric area, brushing with a camel's hair brush or rubber tipped forceps yielded a plentiful amount of petechiae in eleven

out of twenty-three.

The dilated vessels are therefore inclined to rupture after trauma. It was significant that petechial hemorrhages were most prevalent in the region of the small collecting venules where dilation was most noticeable and blood flow almost stopped.

These authors suggested that lack of ascorbic acid may produce a hypotonicity of the peripheral network by disturbing the vasotonic mechanism of the adrenal glands. That scurvy produces a sharp decrease in adrenal ascorbic acid content has been reported by Bessey, Menten and King (1944), Sayers and Sayers, Liang and Long (1946) and Lowenstein and Zwermer (1946). Whether the adrenal function is actually depressed by lowered Vitamin C content is still in question. Banerjee and Glosh (1946) discovered a significant rise in adrenaline content and increase in size of the adrenals in scorbutic animals (guinea pigs), but reported no vascular changes.

The adrenocorticotropic hormone of the pituitary may play an indirect part in producing vascular effects. Sayers et al. (1944) revealed evidence that the adreno-

tropic hormone of the anterior pituitary governs the secretory activity of the adrenal cortex. This mechanism has proven to be very sensitive. In 1945 and 1947, these authors further stated that pituitary adrenotropic hormone initiated the reduction of adrenal ascorbic acid.

### 5. Hesperidin and Rutin

In 1936, Szent-Gyorgi described a substance which reduced hemorrhages in scorbutic guinea pigs and induced longer survival. The material was contained in a fraction of citrous fruits (without ascorbic acid). He called this active portion citrin or vitamin P due to its influence on capillary permeability.

Evidence for the existence of vitamin P was presented by Bourne (1943). Guinea pigs given a scorbutogenic diet with ample ascorbic acid added, still revealed an increase in the fragility of the cutaneous capillaries. The therapeutic value of citrin was also established. Scarborough (1945) demonstrated that this vitamin was capable of increasing capillary resistance, decreasing fragility in man, guinea pig, rat and mouse. Hesperidin

was shown to exhibit vitamin P activity when given by mouth in aqueous suspension.

Parrot and Cotreau (1946) postulated the importance of both vitamin P and vitamin C in the maintenance of normal capillary fragility. In 1948, Cotreau, Gabe, Géro and Parrot found a much greater concentration of ascorbic acid in the organs of the guinea pig when they were given vitamin P along with vitamin C, again establishing their close physiological association. In tests previously performed by Gabe and Parrot (1948), vitamin P appeared to act only in the presence of vitamin C. These authors postulated that the general metabolism of both vitamins as well as their particular effect on capillary fragility closely paralleled each other.

Parrot and Lavollay (1944) supported the hypothesis that the effect of vitamin P on capillary permeability and resistance is felt through the medium of adrenaline. Vitamin P seemed to reduce the destruction of adrenaline within the body.

Haley, Clark and Geisman (1947) using the rat's mesoappendix, applied the following vitamin P

like substances to the membrane: hesperidin chalchone, rutin, and rutin acid succinate. The dilutions used were found to be inactive.

Shanno in 1946 introduced a new drug for the treatment of increased capillary fragility called rutin. It appears to be superior to the hesperidin group in the treatment of: vascular mishaps in those suffering from hypertension, checking some types of pulmonary bleeding, and sustaining the normal degree of capillary fragility. Ambrose and Deeds (1947) found that rutin administration to rabbits shielded them from capillary damage.

### 6. Vitamines D and E

Silver, Stech and Reed (1944) suggested that large doses orally of vitamin D caused a decrease in capillary permeability in adult dogs. The criterion used was a decrease in the disappearance rate of T-1824 from the blood.

Capillary thrombi and a disfunction of the capillary bed in the cerebellum in young chicks were attributed

to lack of vitamin E in the diet of the mother (Pappenheimer and Gaetsh, 1931). Chick embryos hatched from eggs containing inadequate vitamin e showed signs of vascular lesions, edema, small hemorrhages, capillary thrombosis, enlargement of the smaller vessels and proliferation of the capillary endothelium (Adamstone, 1941). Mason (1942) examined sixteen day old fetuses and found the following symptoms of vascular abnormality: stasis, distension of the capillary wall, thrombosis (especially in venous channels), eventually general ischemia and occasionally hemorrhages.

## VII CONCLUSION

A review of the literature has revealed that much controversy exists in regard to the effect of the vitamines and hormones on the peripheral circulation. The achievement of various results is due in part to the failure of most investigators to apply the substance concerned directly to the vascular bed. This method would eliminate metabolic and other chemical changes within the

body which may influence the reaction. Since the capillaries are capable of independent behavior, it appears that the topical application procedure would attain decisive results.

This method however would not disclose any information concerning indirect relationships such as the effect of ascorbic acid on the adrenal cortex which in turn may secrete a substance governing vasomotor tone. This indirect pattern seems to be more prevalent among the vitamines rather than the hormones lending itself therefore less easily to investigation. The development of more adequate techniques with regard to this phase of the problem might incorporate the advantage of highly refined bio-chemical procedures possible employing radioactive materials.

Whatever procedures are applied to the discovery of vitaminogenic or hormonal effects, it would be wise to employ a specific dilution scale of the substance to discover thresholds of activity for the particular tissue preparation.

Extirpation of endocrine glands has been used

successfully by several researchers in determining the negative effects. It seems that the possibilities of a substitution type experiment (ablation with subsequent administration of the specific glandular extracts) offer very interesting and promising results. Of course,this has been a popular type of experiment in many aspects of physiological research, but its applications to this specific problem have been limited.

The more thorough understanding of the hormonal and vitaminogenic influence on small blood vessels is making possible many decisive strides toward the resolution of the more challanging and acute medical problems in cardiovascular pathology such as: hypertension, shock, hemorrhage, edema, menopausal syndromes, etc.

## VIII ABSTRACT

The site of observation, the vascular bed, includes arteries, arterioles, capillaries, venules, veins, arterio-venous anastomoses, and in some tissues, thoroughfare channels. The blood flow through the arteries and artetioles is regulated by the muscular constituents of the vessel walls. Earlier views maintained that the pericapillary cells or the endothelial cells controlled the flow of blood in the capillaries. Recent investigation has favored the concept that a sphincter-like mechanism is present at the capillary origins.

Evidence has been presented for the existence of a physiologically discontinuous plexus of vasoconstrictor and vasodilator fibers. Local responses due to nerve stimulation lended support to the smooth muscle motor-unit concept. As a result of sphincteric activity at the precapillary junctions or different pressure changes within the capillary, intermittency of blood flow occurs regularly in the small vessels. Phases of vasomotion may possibly vary according to local conditions in the tissue, and appear to be dependent on nerve control.

Observations indicate that pitressin helps to control vasomotor tone. According to several investigators this substance is capable of causing constriction, dilation, or both, depending on the tissue and local chemical conditions. Epinephrine is said to cause constriction in most instances although no response or dilation has also been reported, depending on the concentration of the dose. The importance of adrenal cortical hormones in maintaining capillary tonus has been demonstrated. There seems to be agreement concerning the ovarian and testicular hormones. Administration of these always produced dilation.

Thiamine appears to affect the nerve elements, guarding them against degeneration and therefore aiding the control of peripheral circulation. Riboflavin seems to initiate no vascular changes whereas folic acid on the other hand appears to reduce the sensitivity of the cutaneous vessels to estrogens. Niacin administration is followed by dilation of the peripheral network. Ascorbic acid seems to decrease capillary fragility. Its significance in maintaining capillary tone appears to be due to its effect on adrenal cortical secretions. Hesperidin and rutin, assisted by ascorbic acid, help sus-

tain the normal permeability of the capillary walls. Fragmentary information indicated that vitamine D decreases capillary permeability and inadequate vitamine E causes dilation of cutaneous vessels.

Possible avenues of future experimentation have been suggested. Those being used at present were described and evaluated. Much research yet remains to be accomplished to elucidate specific hormonal and vitaminogenic effects on the peripheral circulation. The impetus for further research in regard to this problem is rendered secure because of its vital implications in cardiovascular pathology.

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